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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/408,578	09/29/1999	ARNE HOLM	P63882US0	4214

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JACOBSON PRICE HOLMAN & STERN
D DOUGLAS PRICE
400 SEVENTH STREET NW
WASHINGTON, DC 200042201

EXAMINER
WESSENDORF, TERESA D

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/408,578	HOLM ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1627	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-42,45-65* is/are pending in the application.

4a) Of the above claim(s) *16-42, 45, 60-62, 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *46-59 and63- 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Newly submitted claims 60-62 and 65 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: applicants in the Response of 4/30/01 at page 3, Paper 14, elected to prosecute the sequence of Borrelia burgdorferi (Bb) and biotin as the C moiety.

Since applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 60-62 and 65 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicants argue at page 14 of the 1/18/02 REMARKS that claims 60-62 and 65 are encompassed in the elected species since the claims clarify that one of the peptide sequences is derived from Mycobacterium tuberculosis (MT). It is further argued that throughout the specification, applicants disclose and teach that the presented C and N terminal sequences are different. However, there is nothing in the claims that recites for said difference in the N and C terminal sequences. Applicants cannot read limitations set forth in the specification into the claims.

Furthermore, as stated above, applicants elected Bb as the peptide sequence and no mention was made that the two peptide sequences are different. Accordingly, the peptides drawn to (MT) are withdrawn from consideration and applicants' arguments are not commensurate in scope with the claims.

Status of Claims

Claims 1-15, 43-44 have been cancelled in the amendment of 1/18/00.

Claims 16-42, 45[which depend on cancelled claims (1-15)], 60-62 and 65 are withdrawn from consideration as being drawn to non-elected invention.

Claims 46-59 and 63-64 are pending in the application.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-59 and 63-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the antigenic peptide sequence of Borrelia burgdorferi and

iminodiacetic acid as the bridging group, does not reasonably provide enablement for any type of ligand presenting assembly containing any peptide chain or its homologs or mimics, with any achiral di or tri or tetra carboxylic acid as a bridging group and any type of chemical moiety, target or marker group that elicits an immune response under any given conditions of synthesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enabling disclosure provided in the specification is not commensurate with the scope of the broad claimed method. The instant methods do not only recite a broad step but also cover too numerous undefined variables. The specification is replete with general teachings as to the applicability of the broad method steps to any ligand presenting assembly but the Examples are limited to a specific embodied peptide sequence utilizing a specific bridging groups under specific conditions that result in the desired product. There is nothing in the specification that recites that the single embodied example can be extrapolated to the broad claimed method steps, materials and at any given conditions. Because of the high unpredictability in this peptide conjugate art, it would

require undue experimentation to determine which peptides can employ any bridging group(s) at a given reaction condition to afford the object of the instant invention i.e., prevention of racemization. The high unpredictability in the art is evident from the prior art cited by applicants at page 18 of the instant REMARKS. Applicants recite that "...bridging with half equivalent of suberic acid coupled to one equivalent of lysine...attached to the synthesis resin is slow and takes place over up to 4 days. .....ring formation of longer amino acid sequences may be similar or more difficult requiring activation conditions, which could prevent formation of well-defined products with optically active bridging compounds....."

Applicants' broad steps of synthesis using any achiral dicarboxylic acid is nothing more than an invitation to experiment in the hope that a discovery can be made.

The specification does not teach any tri or tetracarboxylic acid as employed in the instant method.

(It is suggested that applicants limit the scope of the claim to the peptide and dicarboxylic acid disclosed in the Examples).

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Claim 46 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the providing step recited in step (a). It is not clear how said ligands are provided using the solid phase synthesis and unclear as to the phrase "being attached". Is it definitely attached or not? It is further unclear as to the method of step (b) which connotes optional selection of deprotecting any one of the N-terminus of any of peptides in the ligands. This is inconsistent with the specification disclosure wherein more than one ligand is formed after step (c). See, for example, Example 1. The metes and bounds of the number, length and kinds of ligands present in a LPA, within the claimed context, are indefinite. Also, it is not clear within the claimed context what constitutes a presenting

assembly and the context of how such assembly is presented. The process step of "providing" is not a positive, manipulative process step. It is not clear how the "ring structure" is formed by simply adding the carboxylic acid. It is not clear as to the residues linked such that a ring structure is formed, especially since there a number of ligands present in an assembly. (Note the specification recites only dimer formation). It is not evident whether such dimer is a linear or cyclic.

B). Claim 47 step (c') is unclear since claim 6 step © does not recite that the dicarboxylic acid is protected at its N-terminus.

C). Claim 52 is inconsistent and broadens the base claim 46. The base claim does not recite for an additional chemical entity at the N-terminus of the achiral carboxylic acid and recites an N-protected group. The metes and bounds of the chemical entity, target and marker, within the claimed context, are indefinite. The characterization of the chemical entity by its property is indefinite, especially in a process step where reactions are made by the chemical structure of a compound. The terms "enhancing", "being suitable" are relative terms which renders the claim indefinite. These terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in

the art would not be reasonably apprised of the scope of the invention.

D). Regarding claim 53, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). (This rejection is only to point out that said phrase is improper. Enzyme is not the elected species.)

E). Claim 54 is unclear as to the metes and bounds of the B or C epitopes of the peptide sequences, the combination of these epitopes or mimics thereof i.e., what are included or excluded from the claims. This is an omnibus type of claim. Furthermore, it is not clear within the claimed context, "mimics" thereof i.e., in what context the peptide sequences is considered a mimic.

F). Claim 55 is unclear as to the basis by which a peptide sequence is considered to be "important" for an immune response.

G). The metes and bounds of the homologous sequence is unclear especially since it is uncertain whether, in fact said sequence is "capable of reacting with the antibodies or provoking an immune response". Furthermore, it is not clear how a peptide sequence is derived from the OspC protein. Claims 56 and 58.

H). Claim 57 is indefinite in the recitation of LPA since claim 56 recites peptide sequences. Furthermore the language "C-terminal presentation of the C-terminal sequence" is confusing. It is suggested that applicants simply recite that the C-terminal sequence of the peptide is PKKP of OspC.

I). Claim 59 is confusing in its language especially since claim 56 does not recite LPA but peptide sequence. It is suggested that applicants simply recite the amino acids present in the peptide sequence as recited in e.g., claim 63, LPA-1.

J). Claim 64 is a duplicate of claim 58 since the same peptide is being claimed.

Response to Arguments

Applicant's arguments filed 1/18/02 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 46-51 are rejected under 35 U.S.C. 102(a) as being anticipated by Lange et al(J. Pept. Sci.) or 102(b) by Gilon et al (Pept. Chem. , Proc. Jpn. Symp.) for reasons advanced in the last Office action.

Applicants admit that Lange et al relates to the synthesis and activity of dimeric bradykinin (Bk) antagonists containing diaminodicarboxylic acid bridge residues. But argue that the method of Lange et al requires the use of a coupling dicarboxylic acid comprising two chiral centers while the claimed method utilize only achiral dicarboxylic acids that prevents racemization and results in an optically pure product. It is considered that the method of Lange results in an optically pure product as Lange discloses at page 291, col. 2, second paragraph that "……..the protected dimeric decapeptide resins were cleaved and deprotected affording the desired peptides as the only major products……" See further Figure 1. Furthermore, the broadly claimed dicarboxylic acid having numerous substituents does not preclude the dicarboxylic acid of Lange. (Note further the statement in the disclosure, page 13, lines32-33 that with the "exception of glycine all amino acids have a alpha carbon atom including the amino dicarboxylic acids

aspartic and glutamic acid", presupposing that only glycine is achiral.) Thus, the method of Lange would have inherently prevented racemization since the major product produced is the dimeric product.

Applicants admit that the cyclic analogs of Gilon are formed by cyclizing the amino groups of the mentioned amino acids in positions 6 and 9 with dicarboxylic acids, to form the lactam rings. But argue that the lactam rings are different from the products of the present invention in that the cyclization of Gilon is intramolecular as compared to intermolecular cyclization of the present invention. Applicants' argument is not commensurate in scope with the claims. The claims do not differentiate an intra from intermolecular cyclization. There is nothing in the broad claimed method steps that lead to an intermolecular cyclization of the product. In fact, it is not clear whether the dimeric product is in cyclized form.

Accordingly, the method of each of Lange and Gilon, which employs specific products and specific dicarboxylic linking group, anticipates the broad claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 46-59, 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathiesen (WO97/422210) and Tomalia et al (Angew. Chem. Intl. Ed. Engl.) in view of any one of Lange or Gilon for reasons advanced in the last Office action.

It is argued that the combination of the prior art does not disclose forming a macrocyclic ring system by reacting the N-terminal amino group of two identical peptide chains comprising at least 15 amino acids each and still attached to the synthesis resin with an achiral dicarboxylic acid. Applicants' arguments are not commensurate in scope with at least the broad claimed 46. Claim 46 does not recite for a macrocyclic ring and the reaction of two identical peptide chains with the minimum amino acid length of 15. Applicants rely upon the Albert's reference, also cited in the specification, to show the state of the art in bridging techniques i.e., that bridging with half equivalent of 2, 7 bis(Boc amino) suberic acid coupled to one equivalent of

Lysine is slow and takes place over up to 4 days. However, Alberts was published on 1993, which was after the publication date of all of the above-cited references published (1995-1997). The state of the art at the time of applicants' invention is clearly not the Albert's reference rather, the later published work of the prior art references. Accordingly, the combined teachings of the prior art render the claimed invention prima facie obvious.

No claim is allowed.

REASSIGNMENT OF LOCATION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit **1639**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-32179. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

T. D. Wessendorf
Primary Examiner
Art Unit 1627

tdw
October 18, 2002